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Longitudinal Assessment of Health-Related Quality of Life in Preschool Children With Non-CNS Cancer After the End of Successful Treatment

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Background. The aim of the study was to assess Health Related Quality of Life (HRQoL) in preschool cancer survivors during the first 3 years of continuous remission after the end of successful treatment, and to identify predictors of HRQoL. **Procedure.** Parent-reported HRQoL was assessed in 53 preschool children treated successfully for cancer, using the TAPQOL and compared with norm data. Longitudinal mixed models analyses were performed to investigate to what extent demographic and medical variables and parental psychological distress were predictive of HRQoL over time. **Results.** Two months after the end of successful cancer treatment, survivors showed significantly ($P < 0.01$) more problem behavior and anxiety, and scored significantly worse ($P < 0.01$) on sleeping, motor functioning, positive mood and liveliness than the norm. One year after the end of treatment survivors still showed significantly

($P < 0.01$) more anxiety and worse motor functioning. The level of HRQoL in survivors had normalized 2 and 3 years after the end of treatment. Longer duration of treatment, bad prognosis and greater parental psychological distress were associated with worse scores on the Physical Component Score of the TAPQOL. Medical variables and parental psychological distress were not associated with the Mental Component Score. **Conclusions.** Survivors adjusted well to the cancer experience and HRQoL improved with time. Despite overall resilience in survivors over time, physical as well as psychosocial monitoring in follow-up is recommended. Standard aftercare should preferably include psychosocial screening, education, and counseling directed at both survivors and parents. *Pediatr Blood Cancer* 2008;50:1047–1051. © 2007 Wiley-Liss, Inc.

Key words: preschool; quality of life; pediatric oncology; psychosocial; survivors

INTRODUCTION

The diagnosis and treatment of childhood cancer is a dramatic event that affects the daily life and emotional well-being of all family members [1–3]. The enormous increase in survival [4–8] has heightened the need to investigate the consequences of childhood cancer. An increasing number of studies have been directed at assessing Health Related Quality of Life (HRQoL) in long-term survivors, and considerable literature has been devoted to the pediatric patients and their parents during cancer treatment [1,9,10]. Less is known about what happens in the first few years after treatment in the run-up to long-term survivorship. Longitudinal studies are sparse, especially among preschool patients, whereas the number of children with cancer in this age group is relatively high.

The first few years following the end of successful treatment are considered as an important phase in the adjustment to the cancer experience. Coming off therapy is one of the major transitions in care in the practice of pediatric oncology [11]. A longitudinal study was focused on answering the following questions: [1] how is the course of HRQoL of preschool survivors during the first 3 years of continuous remission following the completion of treatment for cancer? [2] To what extent are demographic and medical variables and parental psychological distress associated with HRQoL of preschool survivors during the first 3 years of continuous remission following the completion of treatment for cancer? Although a 5-year period without treatment is commonly considered a criterion of survival, the patients in our study were called survivors because they were in continuous remission in the period approaching long-term survivorship.

METHODS

Procedure

The results presented here are taken from the VOLG-study, a Dutch study on the psychosocial consequences of cancer in childhood, which started in the year 2000 and ended in 2006. From

2000 to 2002, survivors and their parents were recruited from the Emma Children's Hospital at the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Center. The Medical Ethics Committee of the two Dutch hospitals has approved the study protocol.

The inclusion criteria were: [1] age of the survivors 1–18 years, [2] complete remission, [3] end of successful treatment at most 2 months before, and [4] ability to complete Dutch questionnaires. The data of survivors aged 1–5 years ("preschool survivors") with leukemia, lymphoma or solid tumors were used in this article.

Once informed consent had been obtained, the researcher assigned the questionnaire about HRQoL of preschool survivors at random to the father or the mother. The assigned parents completed the questionnaires four to six times depending on the year of inclusion. The first four assessments were used for analyses; approximately 2 months (M1), 1 year (M2), 2 years (M3), and 3 years (M4) after the end of treatment. The data for survivors who relapsed were excluded from analysis from the moment of the relapse.

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Measures

HRQoL was assessed with the *TNO-AZL Preschool Quality of Life* questionnaire for children aged 1–5 years (TAPQOL), which assesses the child's functioning on 12 domains: sleeping, appetite, lungs, stomach, skin, motor functioning, social functioning, problem behavior, communication, anxiety, positive mood, and liveliness. Higher scores indicate better HRQoL [12,13]. Following the method of Ware et al. [14], we used Principal Components Analysis (oblique rotation) at M1 to aggregate all TAPQOL scale scores into two summary scales: Mental Component Scale (MCS) and Physical Component Scale (PCS).

Parental psychological distress was measured using the General Health Questionnaire-30 (GHQ-30). The raw total scale score can be used as an overall index of psychological distress, where higher scores indicate greater distress [15,16].

Medical data were obtained from the survivor's medical record. The prognosis was based on the survival chances at diagnosis as rated by each survivor's oncologist, viz. <25%, 25–75%, or >75%. After the end of treatment (M1), the parents rated their perception of the intensiveness of their child's treatment on a Visual Analogue Scale, from “totally non-intensive” (0, left end of line) to “very

intensive” (10, right end of line). They were also asked to assess the visible consequences of the disease. Their answers were dichotomized to “presence” or “absence” of visible consequences.

Important family events (other than the cancer of the child) during the past year were scored by the parents on a list of 19 such events, including the birth of a child, parental divorce, moving, death of a family member or friend, and decline in financial means. The total score of important family events was dichotomized to “less than two” and “two or more.”

Statistical Analyses

SPSS version 12.0 was used for all analyses. One sample *t*-tests or non-parametric equivalents were performed to test whether the TAPQOL scores of the preschool survivors differed from those in the norm population, at a significance level of 0.01. The seven TAPQOL scales with sufficient internal consistency at every measurement occasion were used for these analyses: problem behavior, anxiety, positive mood, communication, liveliness, sleeping, and motor functioning.

Linear mixed model analysis [17] was performed to examine the course of HRQoL and to what extent demographics, medical

TABLE I. Characteristics of the Survivors

	M1 2 months	M2 1 year	M3 2 years	M4 3 years
N	53	38	23	17
Gender, N (%)				
Girls	27 (50.9)	19 (50.0)	13 (56.5)	10 (58.8)
Boys	26 (49.1)	19 (50.0)	10 (43.5)	7 (41.2)
Age*				
M (SD)	3.9 (1.4)	4.1 (1.3)	4.3 (0.8)	4.8 (0.7)
Range	1.1–5.9	2.0–5.9	2.9–5.6	3.5–5.8
Age at diagnosis*				
M (SD)	2.6 (1.4)	2.1 (1.3)	1.4 (0.9)	1.1 (0.6)
Range at M1	0.3–5.3	0.3–4.5	0.3–3.4	0.3–2.3
Time since diagnosis (months)				
M (SD)	14.7 (9.1)	25.3 (9.1)	34.8 (8.3)	46.3 (7.5)
Range	2.8–29.7	14.1–40.8	26.8–49.9	38.3–61.2
Duration of treatment (months)				
M (SD)	12.6 (9.3)	12.4 (9.2)	10.6 (8.3)	10.3 (7.6)
Range	1.5–25.9	2.1–25.9	2.3–25.5	2.5–25.3
Diagnosis, N (%)*				
Leukemia/lymphoma	24 (45.3)	15 (39.5)	7 (30.4)	4 (23.5)
Solid tumor	29 (54.7)	23 (60.5)	16 (69.6)	13 (76.5)
Treatment, N (%)*				
Chemotherapy	51 (96.2)	36 (94.7)	21 (91.3)	15 (88.2)
Radiotherapy	11 (20.8)	8 (21.1)	6 (26.1)	6 (35.3)
Surgery	26 (49.1)	21 (55.3)	14 (60.9)	11 (64.7)
Autologous bone marrow transplantation	2 (3.8)	2 (5.3)	2 (8.7)	2 (11.8)
Other	2 (3.8)	2 (5.3)	2 (8.7)	2 (11.8)
Prognosis at diagnosis, N (%)*				
<25%	4 (7.5)	4 (10.5)	4 (17.4)	4 (23.5)
25–75%	20 (37.7)	13 (34.2)	10 (43.5)	8 (47.1)
>75%	29 (54.7)	21 (55.3)	9 (39.1)	5 (29.4)
Relapse, N	0	0	0	0
Respondent, N(%)				
Mother	34 (64.2)	26 (68.4)	18 (78.3)	14 (82.4)
Father	19 (35.8)	12 (31.6)	5 (21.7)	3 (17.6)

*Significant differences at <0.1 between survivors with and without TAPQOL data up to M4.

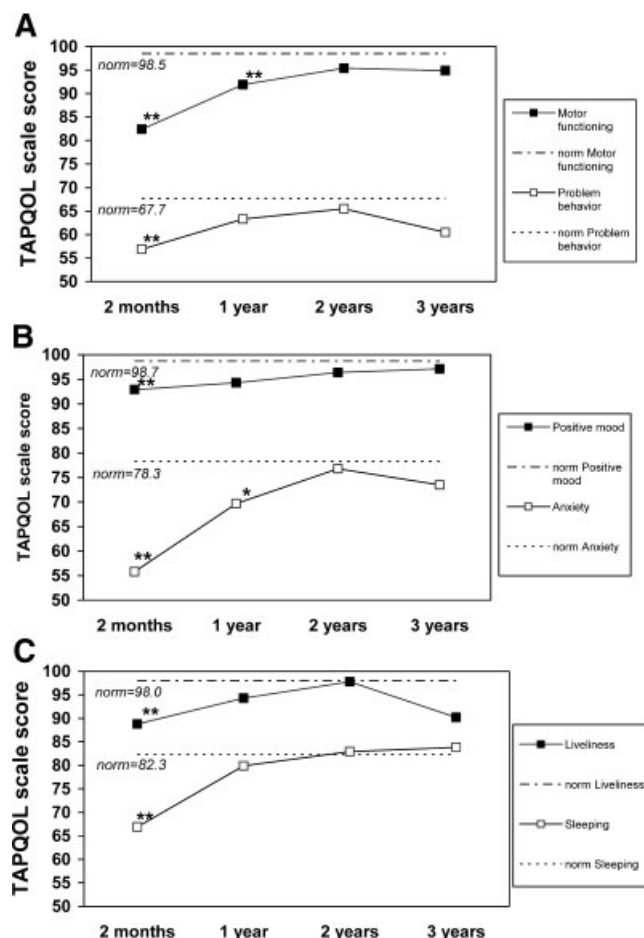


Fig. 1. HRQoL in preschool survivors over measurements occasions: motor functioning and problem behavior (A), positive mood and anxiety (B), liveliness and sleeping (C). Mean TAPQOL scale scores, ranging from 0 to 100 with higher scores representing better HRQoL, that differ significantly from the norm in the general Dutch population of children aged 1–5 years (13) are marked: * $P < 0.01$, ** $P < 0.001$.

variables and parental psychological distress were predictive of HRQoL (PCS and MCS) over time, while controlling for important family events. Measurement occasions were treated as fixed because growth-curve models were not appropriate for these data. Because of the large number of predictor variables in relation to the sample size, preselection was necessary. The initial model consisted of the random intercept M1 and the fixed parameters for measurement occasions M2 to M4. Predictor variables were entered one by one into the initial model. If significant at least at the 0.15 level, variables were selected for the final model. Compound symmetry appeared the best longitudinal covariance structure for PCS, where for MCS an autoregressive structure was more appropriate. We found that it was not necessary to add any first-order interaction effect of measurement occasion with the other predictor variables, at Bonferroni adjusted level of significance.

To facilitate interpretation of regression coefficients, continuous scores were transformed into standard normal scores, expressing deviations from the mean at M1. We considered standardized regression coefficients of 0.1 as small, 0.3 as medium and 0.5 as large after Cohen [18]. For binary coded predictor variables,

regression coefficients of 0.2 can be considered small, 0.5 medium and 0.8 large.

RESULTS

Participants

The parents of 66 consecutive preschool children whose cancer treatment had successfully been ended, were invited to participate in the VOLG-study. The response rate was 81.8% ($N = 54$); 34 mothers and 20 fathers. The 12 survivors whose parents did not participate, did not differ from participating survivors with respect to demographic and medical variables ($P < 0.1$ in t -tests or χ^2 -tests). One survivor was excluded from analyses because she had a brain tumor.

TAPQOL data of 53 survivors were available at M1, 38 at M2 (71.7%), 23 at M3 (43.4), 17 (32.1%) at M4. For 36 survivors TAPQOL data were not available up to M4 (“incomplete data”). The main reason for incomplete data was that if a survivor reached the age of 6 years ($N = 26$, 49.1%), the TAPQOL could not be filled in any longer. Dropout because of non-response was 7.5% ($N = 4$). Furthermore, if a patient suffered from a relapse, the corresponding data from subsequent measurement occasions were excluded from analyses ($N = 6$, 11.3%).

At M1, survivors with incomplete data did not differ ($P < 0.1$) from survivors with data up to M4 (“complete data”), except on one scale: survivors with incomplete data showed less sleeping problems at M1 than those with complete data. As a result of the limited age range of the TAPQOL, differences between incomplete and complete data were found in age and age-related medical variables (Table I).

HRQoL Over Time

Two months after treatment (M1), survivors scored significantly ($P < 0.001$) worse than the norm on six out of the seven TAPQOL scales we used in the analyses (Fig. 1). The differences were large. Compared to the norm, survivors scored worse on problem behavior ($M = 56.9$, $d = 0.7$), anxiety ($M = 55.8$, $d = 1.3$), motor functioning ($M = 82.4$, $d = 3.6$), positive mood ($M = 92.9$, $d = 0.9$), liveliness ($M = 88.8$, $d = 1.1$), and sleeping ($M = 66.9$, $d = 0.9$).

One year after treatment (M2), HRQoL scores have improved though significant differences with the norm were still present on anxiety ($M = 69.7$, $d = 0.4$, $P < 0.01$) and motor functioning ($M = 91.9$, $d = 2.6$, $P < 0.001$). Survivor's level of HRQoL was normalized 2 and 3 years after treatment (M3 and M4). Survivors did not differ from the norm on the Communication scale at any measurement occasion.

Predictors of HRQoL

Parameter estimates from the longitudinal mixed models analyses of survivor's HRQoL are shown in Table II. Apart from the contribution of measurement occasion, Physical HRQoL (PCS) was explained significantly by duration of treatment, prognosis, and parental psychological distress. Longer duration of treatment, poor prognosis ($< 25\%$), and greater parental psychological distress were associated with worse PCS. Apart from measurement occasion, no other variables appeared to be associated significantly with mental HRQoL (MCS). The effects of measurement occasion and prognosis were medium to large, while the effects of duration of treatment and parental psychological distress were small.

TABLE II. Parameter Estimates for Longitudinal Regression Models of HRQoL in Survivors Aged 1–5 Years Predicted by Measurement Occasion, Demographic and Medical Characteristics, and Parental Psychological Distress

Fixed effects	Physical component score (TAPQOL)	Mental component score (TAPQOL)
Measurement (deviation from end of treatment; M1)		
One year (M2)	0.41*	0.41*
Two years (M3)	0.48	0.72**
Three years (M4)	0.52	0.77*
<i>Percentage of explained variance by fixed effects</i>	0.09	0.11
Medical and demographic characteristics		
Gender survivor	—	—
Age survivor	0.02	−0.21
Age at diagnosis	0.04	0.09
Time since end of treatment	—	—
Duration of treatment	−0.13*	0.02
Leukemia or lymphoma (vs. solid tumors)	—	—
Radio- and chemotherapy	—	—
Prognosis < 25%	−0.53*	−0.20
Perceived treatment intensity	—	—
Visible consequences	—	—
<i>Percentage of explained variance by fixed effects</i>	0.24	0.14
Parental data		
Age	—	—
Gender	—	—
Parental psychological distress (GHQ)	−0.13*	−0.12
Important family events (≥2)	—	—
<i>Percentage of explained variance by fixed effects</i>	0.16	0.27
Total number of observations	115	115

* $P < 0.05$; ** $P < 0.01$.

DISCUSSION

Preschool survivors adjusted well to the cancer experience; as time from end of treatment increased HRQoL improved. Longer duration of treatment and poor prognosis seemed to affect physical HRQoL negatively. Survivors with poor prognoses have been treated more intensively which could result in more physical complaints. The greater psychological distress the parents experienced, the worse HRQoL they reported in their child. This finding is in line with results from previous studies on childhood cancer but the direction of the relationship could not be determined [19–22]. We were not able to differentiate between the impact of parental emotions on parental perception of their child's HRQoL and the impact on "real" survivor's HRQoL, because the parents evaluated the HRQoL of their children as well as their own adjustment.

Overall, the variables in the model explained only 26% and 16% of the variance for physical HRQoL (PCS) and mental HRQoL (MCS), respectively. This is not surprising, given the fact that the medical variables were assessed rather roughly and because it was too short after termination of treatment to find late effects of treatment. The limited impact of medical variables on HRQoL has been found in many studies among survivors of childhood cancer [9,10].

There would be other psychosocial factors than assessed in the present study that affect survivors' HRQoL, for example the interaction between the parent and their children. If parents perceive their children's health as very vulnerable, this could lead to overprotection and failing to set age-appropriate limits on the children's behavior, which might have adverse effects for the children [23,24]. Further research is needed to explore these findings, especially because parents of survivors are faced with

uncertainty about the further course of the disease, which might influence their perceptions of their children's vulnerability.

Limitations and Implications

The problem of small sample size is inherent to research on children, especially when children are studied longitudinally, as different age groups need different, age-specific questionnaires. Low power due to small sample size could have contributed to the fact that few variables were found to be predictive of HRQoL. Furthermore, it was necessary to preselect variables for the final analyses. As a result of this, several medical variables were excluded in the final models which could have led to underestimation of the explained variance of the models. Despite the small sample size at the last measurement occasion, longitudinal analyses were possible because linear mixed models analyses incorporates all available data into analysis, including data from survivors that missed one or more measurement occasions.

Another limitation concerns the HRQoL instruments. We used generic HRQoL measures because we wanted to compare the survivors with the general population. The use of cancer-specific instruments is recommended for longitudinal assessments because this kind of instruments is more sensitive to change. Unfortunately, HRQoL instruments translated and validated for Dutch preschool children are not available.

Though most survivors regained a good HRQoL 2 years after the end of successful cancer treatment, there is no reason to lean back because of the known late effects of many treatments [25–29]. Survivors should be followed longer to be able to assess the impact of the late effects on the survivor's HRQoL, physical as well as

psychosocial. It is satisfying that monitoring and screening survivors have become standard aftercare in many hospitals in the last decade. Standard aftercare should preferably include psychosocial screening, education, and counseling directed at both survivors and parents. Providing psychosocial information on the effects of the disease and treatment, and assisting parents in treating the survivors as normally as possible could prevent late psychosocial problems by enhancing re-entry into normal life.

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REFERENCES

1. Eiser C. Children with cancer. The quality of life. Mahwah. New Jersey, London: Lawrence Erlbaum Associates Publishers; 2004.
2. Eiser C. Practitioner Review: Long-term consequences of childhood cancer. *J Child Psychol Psychiatry* 1998;39:621–633.
3. Stevens MCG, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. *Eur J Cancer* 1998;34:694–698.
4. Novakovic BUS. Childhood cancer survival, 1973–1987. *Med Pediatr Oncol* 1994;23:480–486.
5. Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Kalifa C, Barrett A, editors. *Cancer in children: Clinical management*, 4th edition edn. Oxford: Oxford University Press; 1998.
6. Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Barret A, Stevens MCG, Caron HN, editors. *Cancer in children: Clinical management*, 5th edn. Oxford: Oxford University Press; 2005. pp. 1–16.
7. Magnani C, Pastore G, Coebergh J, et al. Trends in survival after childhood cancer in Europe, 1978–1997: Report from the Automated Childhood Cancer Information system project (AGGIS). *Eur J Cancer* 2006;42:1981–2005.
8. Sankila R, Martos Jiménez MC, Miljus D, et al. Geographical comparison of cancer survival in European children (1988–1997): Report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;42:1972–1980.
9. Langeveld NE, Stam H, Grootenhuis MA, et al. Quality of life in young adult survivors of childhood cancer (review). *Support Care Cancer* 2002;10:579–600.
10. Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review). *Support Care Cancer* 2001;9:489–513.
11. Nagel K, Eves M, Waterhouse L, et al. The development of an off-therapy needs questionnaire and protocol for survivors of childhood cancer. *J Pediatr Oncol Nurs* 2002;19:229–233.
12. Fekkes M, Theunissen NCM, Brugman E, et al. Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1–5-year-old children. *Qual Life Res* 2000;9:961–972.
13. Fekkes M, Bruil J, Vogels T. TAPQOL-manual. Leiden: Leiden Center for Child Health and Pediatrics LUMC-TNO; 2004.
14. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: A response. *Qual Life Res* 2001;10:405–413.
15. Goldberg DP, Williams P. A user's guide to the General Health Questionnaire. Windsor: NFER-Nelson; 1988.
16. Koeter MWJ, Ormel J. General health questionnaire: The Dutch application. Amsterdam: Swets Test Services; 1991.
17. Snijders FAB, Bosker RJ. Multilevel analysis. An introduction to basic and advanced multilevel modeling. London: SAGE Publications Ltd; 2004.
18. Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press; 1988.
19. Barakat LP, Kazak AE, Meadows AT, et al. Families surviving childhood cancer: A comparison of posttraumatic stress symptoms with families of healthy children. *J Pediatr Psychol* 1997;22:843–859.
20. Kazak AE, Barakat LP. Brief report: Parenting stress and quality of life during treatment for childhood leukemia predicts child and parent adjustment after treatment ends. *J Pediatr Psychol* 1997;22:249–258.
21. Sawyer MG, Streiner DL, Antoniou G, et al. Influence of parental and family adjustment on the later psychological adjustment of children treated for cancer. *J Am Acad Child Adolesc Psychiatry* 1998;37:815–822.
22. Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. *J Cancer Educ* 1994;9:163–169.
23. Estroff DB, Yando R, Burke K, et al. Perceptions of preschoolers' vulnerability by mothers who had delivered preterm. *J Pediatr Psychol* 1994;19:709–721.
24. Stern M, Karraker K, McIntosh B, et al. Prematurity stereotyping and mothers' interactions with their premature and full-term infants during the first year. *J Pediatr Psychol* 2006 Jul; 31:597–607.
25. Lackner H, Benesch M, Schagerl S, et al. Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years. *Eur J Pediatr* 2000;159:750–758.
26. Oeffinger KC, Eshelman DA, Tomlinson GE, et al. Grading of late effects in young adults survivors of childhood cancer followed in an ambulatory adult setting. *Cancer* 2000;88:1687–1695.
27. Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: Foundations for providing risk-based health care for survivors. *CA Cancer J Clin* 2004;54:208–236.
28. Friedman DL, Freyer DR, Levitt GA. Models of care for survivors of childhood cancer. *Pediatr Blood Cancer* 2006;46:159–168.
29. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Eng J Med* 2006;355:1572–1582.